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Applicant:	James M. Robl et al.	Confirmation No.:	4828
Serial No.:	10/705,519	Art Unit:	1632
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Customer No.:	21559		

Title: TRANSGENIC UNGULATES HAVING REDUCED PRION PROTEIN ACTIVITY AND USES THEREOF

DECLARATION OF DR. YOSHIMI KUROIWA TRAVERSING GROUNDS OF REJECTION OVER GOOD

Under 37 C.F.R. § 1.132 and regarding the rejection of claims 1-6, 25-32, and 35-38 for anticipation by Good et al. (U.S. Patent Publication No. 2002/0069423; hereafter "Good"), I declare:

1. I am an inventor of the subject matter that is described and claimed in the above-captioned patent application. My curriculum vita is attached.

2. To the best of my knowledge, we are the first to produce prion protein (PrP) knockout bovines. In my opinion, the methods of producing PrP knockout cells and bovines disclosed in Good are insufficient to allow one skilled in the art to produce any cells or bovines, and one considering Good alone would not believe that prion knockout cows could be produced.

3. Good intended to isolate the bovine PrP genomic fragment by screening a bovine genomic library using a DNA probe prepared from mouse PrP gene. As stated by Good, "[n]one [of the genomic fragments identified] contained sequences of PrP which could be used to construct a targeting vector." (page 12,

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paragraph 0122). Thus, Good failed in a first attempt even to obtain genomic fragments to begin construction of a targeting vector. In a second attempt, Good decided to amplify the bovine PrP genomic fragment by PCR and constructed one KO vector. That vector is shown in Fig. 5 of Good. Good attempted to combine this vector with genomic DNA. As stated by Good, "it failed." (page 12, paragraph 0126). This vector is the only example that was actually used in an attempt to produce PrP knockout cells. Good failed to produce any experimental evidence that the methods described were operative. Indeed, both actual experiments described in the application were failures.

4. Good also proposed alternative KO constructs, as shown in Fig. 12 and described in Example 2 on page 16. In general, in the field of production of transgenic mammals, it is important for scientists purporting to achieve a result to provide specific information on the reagents and conditions used in order to allow third parties to duplicate any results. Good did not provide sufficient information for one skilled in the art to make the proposed vectors without a substantial amount of experimentation, the success of each step of which is uncertain.

First, Good failed to provide any information in paragraph 0156 on how to determine whether the bovine PrP genomic DNA fragment shown in Fig. 12 would be isolated from the genomic library in a form capable of being successfully employed in a targeting vector. In the art, restriction map information and partial sequence information would be important to exploit an isolated genomic DNA fragment.

Furthermore, the complexity of the genomic library and the number of individual phage to be screened will determine whether the genomic DNA fragment can be isolated. As the genomic DNA fragment necessary for vector construction was not isolated from the genomic library using a ^{32}P-labeled mouse PrP probe in paragraph 0122, it is uncertain whether the genomic DNA fragment could be successfully isolated using the same genomic library and a non-isotopic

probe, as proposed in EXAMPLE 2. Generally, a ^{32}P-labeled probe is more sensitive than a non-isotopic probe. Thus, one skilled in the art would be unsure whether the method described by Good would succeed.

Good further fails to provide any specific guidance in paragraph 0158 on how to construct the targeting vector shown in Fig. 12. The feasibility of constructing the vector as envisioned will depend on the genomic DNA fragment that might be isolated and the kinds of restriction enzymes that will be available for modification of the genomic DNA fragment. Since successful construction of a targeting vector is critical to the success of Good's methods, specific information of how to construct the targeting vector should be provided. A third party could not readily build the vector proposed by Good because of this lack of information on how pieces of the vector would be joined.

Finally, Good fails to provide information on the structure of the targeting vector just before the electroporation in paragraph 0165. For example, no guidance on whether the vector is in circular or linear form is provided, and, if the form is linear, no information is provided on how to linearize the vector. Because circular vectors are not integrated as efficiently as linear vectors, one skilled in the art should be provided with information on both the form of the vector and the conditions under which it is to be transfected into a cell.

5. The processes described in the present application are distinct from those of Good. First, our methods described in the application have been used to produce PrP knockout cells and living bovines. In addition, the specification describes the identification of a genomic PrP DNA fragment (page 46, lines 11-17 and page 55, lines 13-20) and provides exemplary targeting vectors and methods for their construction (page 46, lines 17-30, page 47, lines 12-23, and page 55, lines 20-30), structural information on the vector and methods of animal cloning (page 55, line 30 – page 56, line 26 and page 58, line 28 – page 59, line 19), and a diagnostic PCR to genotype the cells after drug selection (page 56, line 28 – page

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57, line 25 and page 59, line 21 – page 61, line 17). Furthermore, the specification provides data showing that hemizygous and homozygous KO cells were actually produced using the described methods (Example 1, pages 54-61). In addition, as described in my Declaration regarding the enablement of the present application, we have produced PrP knockout bovines using the same methods described in the application. One skilled in the art could reproducibly produce PrP knockout cells and bovines using the methods of the present application.

6. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

11 Sep 2006
Date

Dr. Yoshimi Kuroiwa